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09/955,737	09/19/2001	Rajiv Chopra	16163-015001	9455

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EXAMINER
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STEADMAN, DAVID J

ART UNIT	PAPER NUMBER
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1656

DATE MAILED: 10/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

09/955,737

Applicant(s)

CHOPRA ET AL.

Examiner

David J. Steadman

Art Unit

1656

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 17 July 2006.  
2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.  
3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 12-16, 18-24, 26, 27 and 33-36 is/are pending in the application.  
4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.  
5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.  
6) ☒ Claim(s) 12-16, 18-24, 26, 27 and 33-36 is/are rejected.  
7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.  
8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.  
10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).  
11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some \* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)  
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)  
3) ☐ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_.  
4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_.  
5) ☐ Notice of Informal Patent Application  
6) ☒ Other: Appendix A.

## **DETAILED ACTION**

### ***Status of the Application***

**[1]** Claims 12-16, 18-24, 26-27, and 33-36 are pending in the application.

**[2]** Applicant's amendment to the claims, filed on 17 July 2006, is acknowledged.

This listing of the claims replaces all prior versions and listings of the claims.

**[3]** Applicant's arguments filed on 17 July 2006 are acknowledged. Applicant's arguments have been fully considered and are deemed to be persuasive to overcome some of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

**[4]** The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

### ***Sequence Compliance***

**[5]** This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825; applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). To be in compliance, applicants should identify nucleotide sequences of at least 10 nucleotides and amino acid sequences of at least 4 amino acids in the specification by a proper sequence identifier, i.e., "SEQ ID NO:" (see MPEP 2422.01). If these sequences have not been listed in the computer readable form and paper copy of the sequence listing,

Art Unit: 1656

applicant must provide an initial computer readable form (CRF) copy of the "Sequence Listing", an initial paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification, and a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d). See particularly the disclosed Figure 1A-1EEE of the specification containing a list of atomic coordinates representing the disclosure of an amino acid sequence. When a sequence is presented in a drawing, regardless of the format or the manner of presentation of that sequence in the drawing, the sequence must still be included in the Sequence Listing and the sequence identifier ("SEQ ID NO:X") must be used, either in the drawing or in the Brief Description of the Drawings. See MPEP § 2422.02.

***Claim Rejections - 35 USC § 112, First Paragraph***

**[6]** The written description rejection of claims 12-16, 18-24, 26-27, and 33-34 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in the prior Office action. Newly added claims 35-36 are included in the rejection. Thus, claims 12-16, 18-24, 26-27, and 33-36 are rejected.

RESPONSE TO ARGUMENT: Regarding the examiner's interpretation of "structural coordinates" as defined in the specification at p. 6, paragraph 21, is unreasonable and cannot encompass any structural coordinates. Applicant asserts the structural coordinates are limited to those of Figures 1A-EEE  $\pm$  1.5 Angstrom deviation

Art Unit: 1656

from the backbone atoms "or coordinates modified from those of Figures 1A-1EEE by mathematical manipulation." According to applicant, such coordinates are predictable and do not change the resulting structure represented by the original coordinates and thus the genus of 3-D models of BACE is not widely variant.

Applicant's argument is not found persuasive. As noted by applicant, the specification acknowledges that the structural coordinates can be "modified from those of Figures 1A-1EEE by mathematical manipulation." Such "mathematical manipulation" has been interpreted as encompassing mathematical manipulation of the data of Figures 1A-EEE by an algorithm to generate a homology model. Contrary to applicant's assertion, the claims do not require that the resulting 3-D model of BACE maintains the structure of the original coordinates. Thus, contrary to applicant's position, the 3-D models of BACE encompass widely variant 3-D models of BACE having any sequence of amino acids and any tertiary structure as long as the resulting structure has the recited active site amino acids. In this case, it is highly unpredictable as to whether the resulting homology model(s) will maintain a conformation of a catalytically active BACE polypeptide, which is evidenced by Flower ("Drug Design, Cutting Edge Approaches," Royal Society of Chemistry, Cambridge, UK, 2002), which, addressing the use of homology models for identifying lead drugs, discloses "[p]roblems still exist, however: the fitting together of protein domains in a multi-domain protein, the determination of the most likely conformation of protein loops, the correct positioning of amino acid side chains, flexible ligand docking - to name only a few" (p. 25, middle). The specification discloses only a single representative species of such 3-D BACE models, *i.e.*, the 3-D

Art Unit: 1656

model of BACE having the structural coordinates of Figures 1A-EEE. According to MPEP § 2163.II.2.(a).ii), “[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus.” As such, the single disclosed species is insufficient to be representative of the attributes and features of the genus of 3-D BACE models as encompassed by the claims.

Addressing the BACE and APP polypeptides as used in claims 16, 19, 24, and 27, applicant argues the respective genus of recited BACE and APP polypeptides does not encompass widely variant species. Applicant cites the specification’s disclosed “definitions” of BACE and APP and argues that in view of the disclosure and state of the art, one of skill in the art would recognize the meaning of “BACE” and “APP” as used in claims 16, 19, 24, and 27.

Applicant’s argument is not found persuasive. The examiner acknowledges the “definitions” of BACE and APP at p. 5 of the specification. However, regarding “BACE,” it is noted that the only requirement for the genus of “BACE” polypeptide is that the members of the genus cleave APP at residue 671. Although the specification indicates structural “preferences” for the genus of BACE polypeptides, these “preferences” are non-limiting and thus the genus of BACE polypeptides encompasses any polypeptide having the ability to cleave APP at residue 671. As such, the genus of polypeptides encompasses widely variant structures and the single disclosed species of BACE polypeptides fails to reflect the structural variation among the members of the genus.

Regarding "APP," it is noted that revision history for accession number CAA31380 indicates that accession number CAA31380 has been revised numerous times and it is unclear as to which sequence is referred to by "accession number CAA31380." Further, the specification acknowledges that the genus encompasses conservative mutants of the APP having accession number CAA31380. Thus, the genus of "APP" polypeptides encompasses widely variant structures, including any mutant having "conservative substitutions" of accession number CAA31380. The specification fails to disclose a structure-function relationship between the structures of the genus of conservative mutants of APP accession number CAA31380 as encompassed by the claims and the ability of the genus of BACE polypeptides to cleave an APP polypeptide and the single representative species of APP polypeptides having accession number CAA31380 fails to reflect the variation among the members of "APP" polypeptides as encompassed by the claims.

Thus, at least for the reasons of record and the reasons stated above, a skilled artisan would recognize that applicant was not in possession of all "BACE" and "APP" polypeptides as encompassed by the claims.

Also, it is noted that claims 12 (claims 13-16, 18-19, 33, and 35 dependent therefrom) and 20 (claims 21-24, 26-27, 34, and 36 dependent therefrom) have been amended to require the active method steps of "providing a crystalline composition comprising" BACE and determining the 3-D structure of BACE. For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by

Art Unit: 1656

actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. MPEP § 2163 further states that a "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In this case, the specification discloses only a single representative species of the genus of claimed crystals, *i.e.*, a crystal of the BACE protein prepared as disclosed at pp. 14-15 of the specification in complex with inhibitor SVENStaVAEF having the space group symmetry I222 and having vector lengths  $a=86.627$ ,  $b=130.861$  Å, and  $c=130.729$  Å and  $\alpha=\beta=\gamma=90^\circ$  and the specification discloses only a single representative species of the genus of crystallization methods, *i.e.*, the method disclosed at pp. 14-15, paragraphs 41-44 of the specification. Other than these single disclosed species, the specification fails to describe any additional representative species of the recited genus, which encompasses widely variant species, including crystals of polypeptides that are widely variant in polypeptide sequence, space group, and unit cell dimensions that are unliganded or have any bound ligand, are produced by essentially any method of crystallization. MPEP § 2163 states "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species



Art Unit: 1656

within the genus." As such, the single disclosed species of each genus as noted above fails to describe all members of each genus as encompassed by the claims.

Given the lack of description of a representative number of species, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

**[7]** The scope of enablement rejection of claims 12-16, 18-24, 26-27, and 33-34 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in the prior Office action. Newly added claims 35-36 are included in the rejection. Thus, claims 12-16, 18-24, 26-27, and 33-36 are rejected.

RESPONSE TO ARGUMENT: Regarding the breadth of 3-D models and active sites thereof as encompassed by the claims, applicant argues the examiner's interpretation of "structural coordinates" and "active site" is unreasonable in light of the specification. Applicant asserts the structural coordinates are limited to those of Figures 1A-EEE  $\pm 1.5$  Angstrom deviation from the backbone atoms "or coordinates modified from those of Figures 1A-1EEE by mathematical manipulation." According to applicant, such coordinates are predictable and do not change the resulting structure represented by the original coordinates and thus the genus of 3-D models of BACE and active sites thereof is not widely variant and is no broader than applicant's contribution.

Applicant's argument is not found persuasive. As noted by applicant, the specification acknowledges that the structural coordinates can be "modified from those of Figures 1A-1EEE by mathematical manipulation." Such "mathematical manipulation" has been interpreted as encompassing mathematical manipulation of the data of Figures 1A-EEE by a computer algorithm to generate a homology model. Contrary to applicant's assertion, the claims do not require that the resulting 3-D model of BACE maintains the structure of the original coordinates. Thus, contrary to applicant's position, the claims broadly encompass the use of 3-D models of BACE having any sequence of amino acids and any tertiary structure as long as the resulting structure has the recited active site amino acids.

Regarding the breadth of BACE and APP polypeptides as used in claims 16, 19, 24, and 27, applicant argues the terms "BACE" and "APP" are defined in the specification such that the scope of the claims is no broader than applicant's contribution.

Applicant's argument is not found persuasive. The examiner acknowledges the "definitions" of BACE and APP at p. 5 of the specification. However, regarding "BACE," it is noted that the only defined requirement for a "BACE" polypeptide is that it cleave APP at residue 671. Although the specification indicates structural "preferences" for the genus of BACE polypeptides, these "preferences" are non-limiting and thus the scope of BACE polypeptides encompasses any polypeptide having the ability to cleave APP at residue 671. As such, the scope of BACE polypeptides broadly encompasses any mutant and variant polypeptide that has the ability to cleave APP at residue 671.

Regarding "APP," it is noted that revision history for accession number CAA31380 indicates that accession number CAA31380 has been revised numerous times and it is unclear as to which specific sequence is referred to by "accession number CAA31380." Further, the specification acknowledges that the scope of "APP" polypeptides encompasses conservative mutants of the APP having accession number CAA31380. Thus, the scope of "APP" polypeptides encompasses any mutant having "conservative substitutions" of accession number CAA31380.

Regarding the state of the art, applicant argues, "no one has previously disclosed or suggested the claimed methods." With regards to the novelty of the invention, this issue is addressed below. See rejections under 35 U.S.C. §§ 102 and 103.

Regarding the level of predictability in the art of 3-D protein structural models, applicant argues the claims are not directed to using altered 3-D structures as asserted by the examiner. According to applicant, the claims are limited to the use of a model of BACE having the coordinates of Figure 1A-EEE of the amino acids listed in claim 12 or  $20 \pm 1.5$  Angstrom deviation from the backbone atoms thereof and thus, the application provides sufficient guidance to enable a skilled artisan to practice the full scope of the claimed invention.

Applicant's argument is not found persuasive. As noted above and acknowledged by applicant, the specification states that the structural coordinates can be "modified from those of Figures 1A-1EEE by mathematical manipulation." Such "mathematical manipulation" has been interpreted as encompassing mathematical manipulation of the data of Figures 1A-EEE by a computer algorithm to generate a

Art Unit: 1656

homology model. As such, the claims encompass the use of altered 3-D structures of BACE and, contrary to applicant's assertion, are not limited to the use of a model of BACE having the coordinates of Figure 1A-EEE of the amino acids listed in claim 12 or  $20 \pm 1.5$  Angstrom deviation from the backbone atoms thereof. As noted above, the prior art reference of Flowers acknowledges the unpredictability in the use of homology models for identifying active site ligands, teaching "[p]roblems [with using homology models] still exist, however: the fitting together of protein domains in a multi-domain protein, the determination of the most likely conformation of protein loops, the correct positioning of amino acid side chains, flexible ligand docking - to name only a few" (p. 25, middle). Further, as stated in the prior Office action, Lambert et al. (US Patent Application Publication 2004/0137518) teaches "[p]otential or existent homology models cannot provide the necessary degree of specificity" in the *in silico* design of modulators (p. 3, ¶[0017]), the teachings of which are undisputed by applicant.

Regarding the level of predictability in the art of protein mutation of BACE and APP polypeptides, applicant argues that in view of the knowledge in the field of protein biology and in view of the disclosure, applicant asserts the claimed methods can be practiced with a reasonable degree of predictability.

Applicant's argument is not found persuasive. As noted above, in view of the specification's "definition" of "BACE" and "APP," the claims broadly encompass any mutant and variant polypeptides that have the ability to cleave APP at residue 671 and any mutant having "conservative substitutions" of accession number CAA31380, respectively. Further, it is noted that the level of unpredictability is compounded as the

Art Unit: 1656

claims encompass the use of a combination of mutant BACE *and* APP polypeptides. As stated in the prior Office action and undisputed by applicant, it is highly unpredictable as to the effects of altering the amino acid sequence of a polypeptide and the resulting effects on the activity of the mutant or variant polypeptide. The amino acid sequence of a polypeptide determines the its structural and functional properties. Predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity/utility requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (*i.e.*, expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. The positions within a protein's sequence where modifications can be made with a reasonable expectation of success in obtaining a polypeptide having the desired activity/utility are limited in any protein and the result of such modifications is highly unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, *e.g.*, multiple substitutions. At the time of the invention, methods for isolating or generating variants and mutants of a given polypeptide were known in the art. However, neither the specification nor the state of the art at the time of the invention provided the necessary guidance for altering all BACE and/or APP polypeptides with an expectation of obtaining a polypeptide having the desired activity/utility. At the time of the invention, there was a high level of unpredictability associated with altering a polypeptide sequence with an expectation that the polypeptide will maintain the desired activity/utility. As a representative of such

Art Unit: 1656

unpredictability, the reference of Witkowski et al. (*Biochemistry* 38:11643-11650) teaches that only a single amino acid substitution results in conversion of the parent polypeptide's activity from a beta-ketoacyl synthase to a malonyl decarboxylase (see e.g., Table 1, page 11647).

Regarding the amount of experimentation required, applicant argues the claims are not directed to using altered 3-D structures as asserted by the examiner. According to applicant, the claims are limited to the use of a model of BACE having the coordinates of Figure 1A-EEE of the amino acids listed in claim 12 or  $20 \pm 1.5$  Angstrom deviation from the backbone atoms thereof and thus, the application provides sufficient guidance to enable a skilled artisan to practice the full scope of the claimed invention.

Applicant's argument is not found persuasive. As noted above and acknowledged by applicant, the specification states that the structural coordinates can be "modified from those of Figures 1A-1EEE by mathematical manipulation." Such "mathematical manipulation" has been interpreted as encompassing mathematical manipulation of the data of Figures 1A-EEE by a computer algorithm to generate a homology model. As such, the claims encompass the use of altered 3-D structures of BACE and, contrary to applicant's assertion, are not limited to the use of a model of BACE having the coordinates of Figure 1A-EEE of the amino acids listed in claim 12 or  $20 \pm 1.5$  Angstrom deviation from the backbone atoms thereof. As noted in the prior Office action, while methods of altering a 3-D structure of a protein *in silico* and methods of mutating a polypeptide's sequence were known at the time of the invention, it was not routine in the art to create a substantial number of altered 3-D structures or

Art Unit: 1656

polypeptides as encompassed by the claims without guidance as to which of those is useful in accordance with the asserted utility of the claimed invention, *i.e.*, “in rational drug design methods to identify agents that may interact with active sites of BACE” that “may represent new therapeutics” (specification at p. 1, ¶ [0002]).

Also, it is noted that claims 12 (claims 13-16, 18-19, 33, and 35 dependent therefrom) and 20 (claims 21-24, 26-27, 34, and 36 dependent therefrom) have been amended to require the active method steps of “providing a crystalline composition comprising” BACE and determining the 3-D structure of BACE. The specification, while being enabling for a crystal of the BACE protein prepared as disclosed at pp. 14-15 of the specification in complex with inhibitor SVENStaVAEF having the space group symmetry I222 and having vector lengths  $a=86.627$ ,  $b=130.861$  Å, and  $c=130.729$  Å and  $\alpha=\beta=\gamma=90^\circ$  and the specification discloses only a single representative species of the genus of crystallization methods, *i.e.*, the method disclosed at pp. 14-15, paragraphs 41-44 of the specification, does not reasonably provide enablement for all crystals and methods of crystallization as broadly encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

It is the examiner's position that undue experimentation would be required for a skilled artisan to make the entire scope of the claimed invention. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows:

Art Unit: 1656

(A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

The breadth of the claims: The claims are so broad as to encompass: crystals of any polypeptide that has the ability to cleave APP at residue 671 that are unliganded or have any bound ligand, wherein the crystals have any space group, and/or any unit cell dimensions and any method of crystallization thereof. The broad scope of the claims is not commensurate with the enablement provided by the disclosure. In this case the disclosure is limited to a crystal of the BACE protein prepared as disclosed at pp. 14-15 of the specification in complex with inhibitor SVENStaVAEF having the space group symmetry I222 and having vector lengths  $a=86.627$ ,  $b=130.861$  Å, and  $c=130.729$  Å and  $\alpha=\beta=\gamma=90^\circ$  and the specification discloses only a single representative species of the genus of crystallization methods, *i.e.*, the method disclosed at pp. 14-15, paragraphs 41-44 of the specification.

The state of the prior art; The level of one of ordinary skill; and The level of predictability in the art: The state of the art at the time of the invention acknowledges a **high** level of unpredictability for making a protein crystal with an expectation that it is diffraction-quality. Branden et al. ("Introduction to Protein Structure Second Edition", Garland Publishing Inc., New York, 1999) teaches that "[c]rystallization is usually quite difficult to



Art Unit: 1656

achieve" (p. 375) and that "[w]ell-ordered crystals...are difficult to grow because globular protein molecules are large, spherical, or ellipsoidal objects with irregular surfaces, and it is impossible to pack them into a crystal without forming large holes or channels between the individual molecules" (p. 374). Also, Drenth ("Principles of X-ray Crystallography," Springer, New York, 1995) teaches that "[t]he science of protein crystallization is an underdeveloped area" and "[p]rotein crystallization is mainly a trial-and-error procedure" (p. 1). One cannot predict *a priori* those conditions that will lead to the successful crystallization of a diffraction-quality crystal nor can one predict the space group symmetry or unit cell dimensions of the resulting crystal. See Kierzek et al. (*Biophys Chem* 91:1-20, 2001), which teaches that "each protein crystallizes under a unique set of conditions that cannot be predicted from easily measurable physico-chemical properties" and that "crystallization conditions must be empirically established for each protein to be crystallized" (underline added for emphasis, p. 2, left column, top). Thus, in view of these teachings, a skilled artisan would recognize that it is highly unpredictable as to whether diffraction-quality crystals of other BACE polypeptides as encompassed by the claims can be achieved using *any* crystallization parameters.

The amount of direction provided by the inventor; The existence of working examples:

The specification discloses the utility of the claimed crystal is in the determination of the 3-D structure of BACE and interacting molecules, which, as acknowledged by Branden et al. (*supra*) at p. 374, requires a diffraction-quality crystal. In this case, the specification discloses only a single working example of such a diffraction quality crystal and method for crystallization, *i.e.*, a crystal of the BACE protein prepared as disclosed

Art Unit: 1656

at pp. 14-15 of the specification in complex with inhibitor SVENStaVAEF having the space group symmetry I222 and having vector lengths  $a=86.627$ ,  $b=130.861$  Å, and  $c=130.729$  Å and  $\alpha=\beta=\gamma=90^\circ$  and the specification discloses only a single representative species of the genus of crystallization methods, *i.e.*, the method disclosed at pp. 14-15, paragraphs 41-44 of the specification. Other than these working examples, the specification fails to provide specific guidance regarding making crystals as broadly encompassed by the claims.

*The quantity of experimentation needed to make or use the invention based on the content of the disclosure:* While methods of protein crystallography were known at the time of the invention, it was not routine in the art to screen all polypeptide complexes of any protein that has the ability to cleave APP at residue 671 as encompassed by the claims for those that will yield diffraction-quality crystals using any crystallization conditions as encompassed by the claims.

Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

***Claim Rejections - 35 USC § 102/103***

**[8]** The rejection of claims 12-16, 18-24, 26-27, and 33-34 under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Tang et al. (US Patent 6,545,127) is maintained for the reasons of record and the reasons stated below. Claims 35-36 have been included in the instant rejection. Thus, claims 12-16, 18-24, 26-27, and 33-36 are rejected.

RESPONSE TO ARGUMENT: Applicant argues the claims do not encompass the use of any structural coordinates, but are limited to using the structural coordinates of Figure 1A-EEE  $\pm$  1.5 Angstrom deviation from the backbone atoms. Applicant argues the residues of BACE in the crystal of Tang et al. are amino acids 14 to 454, while the residues of BACE of the instantly disclosed crystal are amino acids 47 to 460 plus 9 amino acids due to a cloning artifact. Thus, according to applicant, the 3-D models of the reference of Tang et al. are not encompassed by the claim as Tang et al. does not disclose or suggest the structural coordinates of Figure 1A-EEE.

Applicant's argument is not found persuasive. The reference of Tang et al. teaches crystallization of human BACE (referred to as memapsin 2 by Tang) co-complexed with a BACE inhibitor (Example 9), determination of the 3-D structure of human BACE (Example 9), a method of identifying a BACE inhibitor using the 3-D structure obtained thereby (columns 13-14, Example 10), synthesis of BACE inhibitors so designed (Example 7), and inhibitor screening assays of BACE using the synthesized inhibitors in the presence of a synthetic peptide substrate (Example 8). In

Art Unit: 1656

this case, there appears to be no dispute that, with the exception of the 3-D model of BACE, the reference of Tang et al. teaches all limitations of claims. The examiner acknowledges that Tang et al. does not appear to teach the structural coordinates of Figure 1A-EEE. However, the claims do not require that the 3-D model have all amino acids of the structural coordinates of Figure 1A-EEE. Instead, the claims only require that the 3-D comprise certain amino acids of the "relative structural coordinates" of Figure 1A-EEE. Applicant appears to take the position that because the residues of BACE in the crystal of Tang et al. are amino acids 14 to 454, while the residues of BACE of the instantly disclosed crystal are amino acids 47 to 460 plus 9 amino acids due to a cloning artifact, the 3-D BACE structure of Tang cannot be encompassed by the claims. However, it is noted that the residues required to present in the 3-D model in the claimed methods lie within the range of amino acids of the 3-D model of Tang et al. Put another way, the recited amino acids of the 3-D model of BACE in the claims are present in the 3-D model of Tang et al. Since the Office does not have the facilities for examining and comparing applicant's 3-D model of BACE with the model of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed method and the method of the prior art (i.e., that the 3-D model of BACE of the prior art does not possess the same material structural and functional characteristics of the recited 3-D model of BACE). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald et al.*, 205 USPQ 594. As such, absent evidence to the contrary, the 3-D model of Tang et al. is the same as the 3-D model of BACE as

Art Unit: 1656

encompassed by the claimed methods. As such, the reference of Tang et al. anticipates the claims as written.

***Claim Rejections - 35 USC § 103***

[9] The rejection of claim(s) 9-19, 21, and 31-33 under 35 U.S.C. 103(a) as being unpatentable over Sauder et al. (cited in the IDS filed on 19 April 2002) in view of Anderson et al. (US Patent 5,942,400); the rejection of claim(s) 9-15, 17-18, 20-23, and 25-26 under 35 U.S.C. 103(a) as being unpatentable over Balaji et al. (US Patent 5,579,250) in view *In re Gulack* 217 USPQ 401 (Fed. Cir. 1983); and the rejection of claim(s) 16, 19, 24, and 27 under 35 U.S.C. 103(a) as being unpatentable over Balaji et al. in view *In re Gulack* 217 USPQ 401 (Fed. Cir. 1983) as applied to claims 9-15, 17-18, 20-23, 25-26, and 31-34 and further in view of Anderson et al. are withdrawn in view of the amendment to the claims. None of Sauder et al., Anderson et al., or Balaji et al. teaches "providing a crystallization composition comprising" a BACE polypeptide as required in claims. As such, the combination fails to teach all limitations of the claimed invention. Even assuming *arguendo* the combination suggests the use of a BACE crystal to obtain structural coordinates for molecular modeling, none of the references alone or in combination enables crystallization of a BACE polypeptide.

[10] Claim(s) 12-16, 18-24, 26-27, and 33-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tang et al. (US Patent 6,545,127) in view of *In re Gulack* 217 USPQ 401 (Fed. Cir. 1983). See MPEP §§ 2144 and 2144.04 regarding legal precedent

Art Unit: 1656

as a source of rationale for rejection under 35 U.S.C. § 103 and see MPEP §§ 2106.IV.B.1.(b) and 2106.VI regarding determination of whether descriptive material is functional or non-functional. The claims are drawn to a method for identifying an agent that interacts with an active site of BACE. This rejection is necessitated by applicant's amendment to require the step of "providing a crystalline composition comprising" BACE in claims 12 and 20.

The reference of Tang et al. discloses the teachings as described above. The method as taught by Tang et al. is the claimed method, only missing the structural coordinates of Figure 1A-EEE.

In Gulack, the court held that nonfunctional descriptive material in a claim does not distinguish the prior art in terms of patentability. The key factor in analyzing the obviousness of these claims over the prior art is the determination that the computer algorithm used to identify compounds that may bind BACE is a known algorithm and is unmodified. If the difference between the prior art and the claimed invention as a whole is limited to descriptive material stored on or employed by a machine, it is necessary to determine whether the descriptive material is functional descriptive material or nonfunctional descriptive material. In this case, the BACE structural coordinates as disclosed in Figure 1A-EEE are non-functional descriptive material and the method uses a known unmodified computer algorithm. Data, which are fed into a known algorithm whose purpose is to compare or modify those data using a series of processing steps, do not impose a change in the processing steps and are thus nonfunctional descriptive material. A method of using a known comparator for its known purpose to compare data

Art Unit: 1656

sets does not become nonobvious merely because new data becomes available for analysis. Nonfunctional descriptive material cannot render nonobvious an invention that would have otherwise been obvious.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to perform rational drug design as taught by Tang et al. to identify an agent that binds to BACE and optionally including the steps of obtaining or synthesizing the compound and contacting the compound with BACE protein, wherein only non-functional descriptive material is additionally present in the claims, which do not distinguish the claimed methods from those taught by Tang et al. according to In re Gulack.

**RESPONSE TO ARGUMENT:** To the extent applicant's arguments relate to the instant rejection, the arguments are addressed below.

Applicant argues the claims now require the limitation of providing a crystalline composition comprising BACE and that none of the cited references provides this teaching or suggestion.

Applicant's argument is not found persuasive. With the exception of the structural coordinates of Figure 1A-EEE, the reference of Tang et al. teaches all limitations of the claims. Applicant may argue that because the Tang et al. reference fails to teach the structural coordinates of Figure 1A-EEE, the claims are free of the prior art of record. However, as noted above, the only difference between the method of Tang et al. and the method claimed herein as a whole is limited to nonfunctional descriptive material. In this

Art Unit: 1656

case, "[n]onfunctional descriptive material cannot render nonobvious an invention that would have otherwise been obvious." See MPEP 2106.VI. See also MPEP 2106.IV.B.1.(b) regarding the determination of whether descriptive material is functional or non-functional.

### ***Conclusion***

**[11] Status of the claims:**

Claims 12-16, 18-24, 26-27, and 33-36 are pending.

Claims 12-16, 18-24, 26-27, and 33-36 are rejected.

No claim is in condition for allowance.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.



Art Unit: 1656

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



David J. Steadman, Ph.D.  
Primary Examiner  
Art Unit 1656

Art Unit: 1656

## APPENDIX A

Revision history for CAA31830

GI	Version	Update Date	Status	I	II
871360	1	<u>Mar 8 2006 1:36 PM</u>	Live		
871360	1	<u>Aug 5 2003 12:10 AM</u>	Dead		
871360	1	<u>Oct 15 2002 5:27 PM</u>	Dead		
871360	1	<u>Mar 9 1999 3:05 AM</u>	Dead		
871360	1	<u>May 29 1996 3:10 AM</u>	Dead		
871360	1	<u>Jun 23 1995 11:03 AM</u>	Dead		
35600	0	<u>Apr 4 1995 2:06 AM</u>	Dead		
35600	0	<u>Nov 30 1994 8:32 PM</u>	Dead		
35600	0	<u>Sep 1 1993 4:49 AM</u>	Dead		
35600	0	<u>Apr 21 1993 6:19 AM</u>	Dead		

Accession CAA31830 was first seen at NCBI on Apr 21 1993 6:19 AM